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**Written testimony**

**Before the**

**United States House of Representatives**

**Committee on Government Reform**

**Public Hearings on**

**"The Roles of FDA and Pharmaceutical Companies in**

**Ensuring the Safety of Approved Drugs, Like Vioxx."**

**May 5, 2005**

I am honored to testify in the May 5, 2005 House Government Reform hearings on "The Roles of FDA and Pharmaceutical Companies in Ensuring the Safety of Approved Drugs, Like Vioxx." I am a Resident Scholar at the American Enterprise Institute for Public Policy Research, where I have conducted research on pharmaceutical markets and other topics. The views I present are my own and do not necessarily represent those of the American Enterprise Institute. Much of this testimony draws on an unpublished article written by my colleague Ximena Pinell and me, which covers the Vioxx incident and its significance in considerable detail (Calfee and Pinell 2005).

**1. FDA's Surveillance of Post-approval Drug Safety**

Any assessment of post-approval drug safety surveillance must begin by acknowledging the extraordinary difficulty of that task. Our health care system is highly decentralized with thousands of individual physicians, clinics, and hospitals, most of which do not share data. Patients often receive care from more than one organization, and they self-administer over-the-counter (OTC) drugs, many of which compete directly with powerful prescription drugs. The tort liability system undermines incentives of physicians and others to report in a timely and forthright manner events that might involve drug safety but might also involve error or perceived error (Leape 2002). Finally, many adverse drug events carry ambiguous implications because of the difficulty of separating inherent drug safety from patient misuse, physician error, hospital error, and above all, the difficulty of administering many drugs–including such common drugs as insulin, heparin, and warfarin–which are both very useful and very dangerous (Gurwitz, et al. 2003). The pervasive problems in monitoring the safety of drugs or indeed the safety of any important component of health care have been widely recognized (Bates 1998; Leape 2002).

The FDA appears to recognize these problems and seems eager to address them by encouraging better record-keeping and communication in the health care system, more efficient methods for reporting potential problems to the FDA, increased attention to safety during pre-market testing, and enhanced post-approval monitoring. In March 2005, the FDA issued a series of guidances for the pharmaceutical industry on pre-market risk assessment, post-approval monitoring, and pharmacovigilance (the surveillance of side-effects) and pharmacoepidemiology (the study of a drug's efficacy and safety using large data sets) (FDA 2005a, b, c, d). These initiatives address two fundamental components of drug safety: how drugs work in clinical practice, and how to communicate drug safety information and practices to physicians and patients.

The process of communicating about drug safety is fraught with difficulties such as over-warning and consequent under-use of valuable drugs. This was pointed out in a 2003 speech by former FDA Commissioner Mark McClellan. After describing a

litigant's attempt to add a suicide warning to an antidepressant drug's label despite the FDA's rejection of it three times on scientific grounds, McClellan warned, "the drawing of unwarranted attention to an unproven but serious risk could lead to undertreatment of depression." The problem is also widely appreciated in the medical community. An example is the American Psychiatric Association's strong opposition to the "black box" warning added to the labels of popular antidepressants, which, by deterring their use, "would put seriously ill patients at grave risk" (APA press release 2004).

It is unlikely that the FDA now performs these difficult tasks as well as they can be done. On the other hand, clear paths to unambiguous improvement are not well established. Although I would be the last person to argue that the FDA does its overall job in an unimpeachable manner, I would nonetheless warn against forcing the FDA into abrupt changes in its handling of the safety of approved drugs. In particular, the creation of an independent drug safety board insulated from the FDA's drug approval and oversight staff would severely hamper the already difficult task of balancing the costs and benefits of new drugs (for reasons discussed below).

**2. The Cox-2 class of NSAIDs**

Merck's Vioxx (rofecoxib) is a member of the class of drugs known as Cox-2 inhibitors. The Cox-2s are part of the larger class of NSAIDs (non-steroidal anti-inflammatory drugs), which includes such popular pain relievers as Alleve (naproxen), Advil (ibuprofen), and several prescription-only drugs, along with the original NSAID, aspirin. The traditional NSAIDs are probably the most-used of any drug category worldwide, especially for treating arthritis pain, but they often cause upper gastro-intestinal (G.I.) ulcers and bleeding. This can cause pain and even death. The most reliable estimate of the death toll from NSAID use in the United States is between ten and twenty thousand deaths annually (Wolfe, Lichtenstein, and Singh 1999).

The Cox-2s were developed after researchers discovered some fifteen years ago that NSAIDs suppressed both the Cox-1 enzyme, which is protective of the stomach and the rest of the G.I. system, and the Cox-2 enzyme, which reinforces inflammation and

thus causes pain. This insight suggested that if research firms could develop selective NSAIDs, which suppress mainly the Cox-2 enzyme, those drugs could offer pain relief with less G.I. harm. The arrival of the first Cox-2 inhibitors, Celebrex (celecoxib; Pfizer) and Vioxx, was greeted with enthusiasm by the medical community, especially those who treat arthritis: "That these COX-2 selective inhibitors have become so successful within the same year of their launch attests to the perceived need for novel agents that can control the signs and symptoms of inflammatory diseases, but with minimal risk of gastrointestinal side effects" (Whittle 2000).

It turned out that the Cox-2 enzyme is implicated in cancer as well as inflammation, which opened a line of research into the Cox-2 inhibitors as cancer preventives or treatments (Chau and Cunningham 2002). Also, inflammation has been identified as important in conditions other arthritis, including Alzheimer's and coronary heart disease. Hence pharmaceutical firms pursued numerous clinical trials on cancer prevention and other illnesses as well as on arthritis treatment.

On September 30, 2004, Merck withdrew Vioxx from the market without consulting with the FDA after results from a nearly completed three-year clinical trial in cancer prevention revealed a statistically significant increase in heart attacks and other adverse cardiovascular events such as strokes (Bresalier 2005). Merck took this action because it believed that Vioxx was unique among the Cox-2 inhibitor class of drugs in its cardiovascular risk profile (Merck 2004).

A storm of criticism descended upon both Merck and the FDA for not having taken various actions–including the withdrawal of Vioxx–months or years earlier (e.g., Topol 2004; *Lancet*, Dec. 4, 2004). Critics included leading medical journals and academic medical researchers, newspaper editorials and op-ed writers, and participants in Congressional hearings. I believe that as events proceeded and research results were compiled, much of this criticism proved to be excessive if not unfounded.

## 3. What Should Merck Have Done Earlier?

### A. Should Merck Have Conducted More Studies of Cardiovascular Risk?

The clinical trials that provided the foundation for FDA approval of Vioxx had revealed no excess cardiovascular problems in comparison to traditional NSAIDs. There were some signs of risk relative to placebos–i.e., relative to the use of no pain reliever at all–but as FDA staff noted at the time, this was true of all NSAIDs (Pelayo 1999). The large-scale VIGOR trial, published in November 2000 (more than a year after Vioxx was approved for marketing), revealed dramatically lower G.I. problems but unexpectedly showed a significantly higher level of heart attacks and strokes (Bombardier, et al., 2000). The implications of this result were far from clear. A substantial fraction (38 percent) of heart attacks was in patients for whom low-dose aspirin was indicated (due to history of heart attacks or other cardiovascular complications) but who failed to take it (the trial avoided accepting patients on aspirin). For other patients, heart attack rates did not differ significantly. Because heart attacks were not a pre-defined endpoint in the VIGOR trial, because Vioxx had been compared to naproxen, a traditional NSAID, rather than to a placebo, and because other trials involving both Vioxx and Celebrex had not revealed significant cardiovascular problems, it was by so means obvious that Vioxx would in fact cause excess heart attacks compared to placebos. Obvious alternatives were that the result was partly a statistical fluke (always possible when selecting a non-predefined endpoint for analysis) or that the comparator, naproxen, was instead cardio-protective. Subsequent research strongly suggested that naproxen is at least moderately cardio-protective (Dalen 2002; Juni, et al. 2004).

A natural question, raised in the medical literature and elsewhere (cf. Mukherjee, et al. 2001) was whether Merck should immediately mount another clinical trial, presumably against a placebo instead of another NSAID, in order learn with more certainty whether Vioxx causes heart attacks. But what trial to run? Considerable debate centered on what population to study: patients with high risk for heart attacks and strokes (whose comorbidities and multiple drug use would greatly complicate the trial), or some other population? Unless several large trials were launched, crucial questions would

remain. Yet running even a single trial with sufficient power to detect a doubling of a small long-term risk would involve thousands of patients spread across scores or hundreds of medical practices, at a cost of tens of millions of dollars or more, and require one to three years for design, execution and analysis.

An equally important question was which drug to test. Vioxx was probably not the best target. As the FDA has repeatedly pointed out, traditional NSAIDs had never been subjected to large, long-term trials like VIGOR.[1] The fact that NSAIDs reduce inflammation, which is implicated in heart attacks, suggests that they could prevent heart attacks. But analysis of the biological mechanisms involved in NSAIDs generates ambiguous results, suggesting that Cox-2s and other NSAIDs could facilitate rather than impede the processes that lead to heart attacks (Fitzgerald 2001). As one researcher pointed out in *The Lancet*, the common observation that arthritis patients have more heart attacks has been seen as implicating arthritis itself; but it is impossible to rule out the possibility that the heart attack risk derives instead from the extremely common use of NSAIDs by arthritis patients (Scott and Watts 2005). Because most of what was already known about NSAIDs and cardiovascular disease had come from Cox-2 clinical trials, it probably made more sense to start work on traditional NSAIDs. This line of research would in fact be recommended by the FDA in its April 7, 2005 NSAID initiative (FDA press release April 7, 2005). Given the fact that none of the traditional NSAIDs are under patent, such trials would have to be sponsored by NIH or another public source.

It so happened that in 2001, Merck was already planning a large, placebo-controlled trial (called APPROVe) to test whether Vioxx could prevent colorectal cancer. By adding cardiovascular endpoints, the APPROVe trial could detect significant cardiovascular risk. Given these circumstances, it is hard to see why Merck had an obligation to do more than run the very expensive APPROVe trial with its cardiovascular

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[1] *New York Times*, October 19, 2004: "Dr. Janet Woodcock, acting deputy commissioner for operations at the F.D.A., said in a speech at the American College of Rheumatology meeting in San Antonio yesterday that 'at this point we don't have any definitive evidence' that the COX-2 inhibitors as a class are more risky than older painkillers like ibuprofen and naproxen."

endpoints. Events have vindicated this view. The tight focus of academic and other critics on Vioxx and Merck proved misplaced. When the FDA issued its most definitive report on NSAIDs (Jenkins and Seligman 2005) and undertook a major initiative in the NSAID market on April 7, 2005, it made perfectly clear that what began as a Vioxx incident was in fact an NSAID issue. It stated that there is no convincing evidence that Vioxx is more dangerous than other Cox-2s in terms of cardiovascular risk or that Cox-2s as a class are more dangerous than traditional NSAIDs. The agency therefore required cardiovascular warnings for all NSAIDs and urged NIH and other agencies to undertake large-scale clinical trials of traditional NSAIDs (Jenkins and Seligman 2005; FDA press release Apr. 7, 2005).

**B. Should Merck Have Curtailed or Redirected Consumer Advertising?**

Another issue is Vioxx advertising, especially direct-to-consumer (DTC) advertising. Although commentators have often assumed that DTC advertising played a large role in the uptake of Cox-2s, this is far from clear from the factual record. Total Cox-2 DTC advertising in the year 2003 was $165 million (*New York Times* Dec. 21, 2004) compared to sales of $4.4 billion (IMS Health, IMS National Sales Perspectives). Such a small advertising-to-sales ratio suggests limited returns to advertising.

Also instructive is experience abroad. In Canada, the arrival of the first two Cox-2s, Celebrex and Vioxx, caused a 50 percent increase in NSAID prescribing (Mamdani, Rochon, Laupacis, and Anderson 2002). Vioxx was reportedly the fastest selling new drug in the history of the U.K. health system (Emery, Hawkey, and Moore 200**1**), although its sales remained small by U.S. standards. In Australia, the first two Cox-2s, Celebrex and Vioxx, gained sales so rapidly as to cause an immediate fiscal "calamity" in the government-subsidized drug benefit. None of these nations permit DTC advertising. As in the U.S., the rapid uptake of Cox-2s reflected the initial enthusiasm of medical experts and innate consumer preferences more than the force of advertising.

A related issue is whether Vioxx and competing Cox-2s were used primarily by patients at high risk for upper G.I. problems. In general, Cox-2 usage extended well

beyond that group. This is partly because some patients encounter serious G.I. bleeding with little warning in their personal histories, as reflected in prominent practice guides that recommended Cox-2s as first-line arthritis pain therapies (American Pain Society 2002; American Geriatric Society 2002). But other factors essentially guaranteed broad usage. Vioxx and other Cox-2s offer simplified dosage (one or two pills a day instead of two or more pills several times a day), with less need to take additional drugs to prevent heartburn or ulcers. For some patients, a Cox-2 provides superior pain relief (reflecting individual differences in patient response to drug therapy). With most patients paying only a small co-payment, Cox-2s were clearly attractive to a broad range of users. Thus an early Australian study found that more than two-thirds of Cox-2 patients had not previously been prescribed a traditional NSAID, and up to 60 percent had not been prescribed *any* painkiller in the preceding year (Kerr, et al, 2003). A Canadian study of Cox-2 usage found only a moderate tendency toward patients at high G.I. risk despite a requirement that physicians document a G.I.-related need (Mamdani, Rochon, Laupacis, and Anderson 2002).

Oddly enough, advertising was strongly limited in its ability to target Cox-2 usage. DTC advertising was banned altogether in Canada and Australia, of course. But even in the U.S., FDA rules prohibited manufacturers from advertising the G.I. benefits of Cox-2s. Such benefits had not been documented (at least, not to the FDA's satisfaction) in the trials that supported FDA approval. G.I. protection was never on the FDA-approved Celebrex label, and even after the APPROVe trial, Merck still had to warn patients of G.I. risks because Vioxx had reduced, but did not entirely eliminate, G.I. complications. Thus neither consumer advertising nor promotion directed at physicians could easily target high G.I. risk patients.

**4. What should the FDA have done earlier?**

The common argument that the FDA should have moved rapidly to force Vioxx off the market or require vigorous warnings and/or large-scale clinical trials (e.g., Topol 2004; *Lancet*, Dec. 4, 2004) has proved largely unfounded. Consider the question of

whether the FDA should have required a strong cardiovascular warning shortly after the VIGOR results were released in 2000. One should take into account the fact that the VIGOR results were widely discussed and debated in the medical community. Several Cox-2 and NSAID reviews published during this period (e.g., Dalen 2002; Bjarnason, Takeuchi, and Simpson 2003; and Whittle 2003) all reached roughly the same set of conclusions: The Cox-2s provided important G.I. protection. Most trials had not revealed significant cardiovascular problems, but at least one large trial (VIGOR) had. The VIGOR results might have been caused by a cardioprotective property of naproxen, but Vioxx itself might also have been the problem. Thus possible CVD side-effects should be monitored even as Cox-2s are prescribed for their original purpose of providing pain relief while reducing G.I. side-effects.[2] These ad hoc reviews were complemented by periodic updating of practice guidelines issued by professional organizations and practitioner-oriented journals (e.g., American Pain Society 2002; American Geriatric Society 2002; American College of Rheumatology treatment guidelines in Schnitzer 2002). It seems clear that the most important data on cardiovascular side-effects associated with Vioxx were widely disseminated and digested in the medical community. One indication of the market effects is the fact that after an extraordinarily rapid uptake in the first two years, Cox-2 sales were essentially flat in 2001 through 2004 (Calfee and Pinell 2005, table 1).

Given these circumstances, it seems unlikely that a quicker addition of a cardiovascular warning to the Vioxx label would have significantly improved medical practice. In fact, it might have impeded best practices; the FDA eventually concluded that even with the APPROVe results in hand, there is no compelling evidence that other Cox-2s or other NSAIDs are significantly safer than Vioxx in terms of adverse cardiovascular side-effects.

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[2] Bjarnason, et al. 2003 noted, "The incidence of these [cardiovascular] side effects is very unlikely to outweigh the benefits of the improved gastrointestinal tolerability."

For much the same reason, it would have been a mistake for the FDA to have forced Vioxx off the market because of the VIGOR findings. Doing so would have pushed prescribing toward other Cox-2s or more likely, traditional NSAIDs. Again, there was little evidence at the time (and little evidence now) that this would have benefited patients.

I have already discussed the question of whether Merck should have conducted additional clinical trials to assess cardiovascular side-effects. The same reasoning applies here. Just as it made little sense to push forward with trials of Vioxx instead of other NSAIDs, the FDA had little reason to force Merck to launch such trials, especially in light of the fact that Merck was already preparing to start a cancer trial that would include cardiovascular endpoints.

**5. Impact of the Vioxx episode on the FDA**

The FDA has long been criticized by economists and others for being too cautious in approving new drugs. An excessive emphasis on safety is perfectly understandable given the incentives faced by FDA staff. If the staff is too slow to approve a new drug, almost no one notices because few people know enough to assess what patients have been losing. But if a drug gets approved and then runs into safety problems, public awareness is widespread and quickly expanded through the news media and other sources. If there is an institutional bias at the FDA, it is toward excessive emphasis on safety in approving new drugs and leaving them on the market, rather than a lax attitude toward safety.

Some FDA critics have cited the Vioxx withdrawal as evidence that even if the FDA has sometimes been too cautious, the situation has changed because a substantial proportion of FDA funding comes from industry user fees. The argument is that the FDA has gotten too close to the industry and therefore inappropriately discounts safety in order get drugs on the market sooner and keep them there (e.g., Topol 2004). Quite aside from the fact that the PDUFA law that mandates user fees simply requires the FDA to make decisions faster–but not to make decisions more favorable to the industry–it is clear from the Vioxx episode that the incentives for FDA staff to maintain at least reasonable drug

safety standards–or even much higher standards–remains largely undisturbed. The fusillade of criticism directed at the agency over Vioxx and Cox-2s–especially from its most reliable base of support, the academic medical community and the most prestigious medical journals–vastly exceeds any criticism it has received in recent years for being too slow to approve new drugs or too quick to remove them.

Thus the Vioxx episode has probably made it more difficult for the FDA to do its job and has probably pushed the FDA even further than usual toward excessive caution in guiding manufacturers through clinical trials and the approval process. This is reflected partly in institutional changes such as the creation of Drug Safety Oversight Board that includes outside experts (FDA, February 15, 2005 Press release). This body is purely advisory and will not have authority to relabel or withdraw drugs. Whether it will reinforce the agency's natural tendency toward over-caution remains to be seen. But at least it is vastly superior to the creation of a fully independent board with power to remove drugs or change their labeling, as some have proposed to do through legislation (e.g., *Lancet*, Feb. 26, 2005). An independent board would necessarily impede the routine balancing of costs and benefits of drugs that must occur as post-approval data provides new information on both unexpected problems and surprisingly high (or low) efficacy. Nor would an independent board avoid be immune to having an interest in approved drugs. The board would necessarily make repeated rulings on the same drug in response to a series of safety alarms. This would leave board members with the same stake in their past decisions that the FDA's drug approval staff now have, but without an off-setting responsibility to assure that useful drugs remain available to physicians and patients.

The Vioxx episode appears to have led the FDA to take other measures that could prove harmful to the development and use of valuable new drugs. The agency has begun to require more warnings, especially the "black box" warnings that can dominate prescribing information (an example being the April 11 imposition of black box warnings on seven anti-psychotic drugs; *Wall Street Journal*, April 12, 2005). As was pointed out by professional physician organizations in connection with the required black box

pediatric suicide warning for the SSRI class of antidepressants, too many warnings can cause as much harm as too few warnings, leading to under-use of drugs that treat or prevent conditions that are themselves dangerous (APA 2004). News reports suggest that is exactly what has happened (*New York Times*, September 16, 2004).

The FDA has also moved aggressively to make emerging results from clinical trials available to physicians and the general public via a Drug Watch Web Page (FDA, February 15, 2005 Press release). Although this initiative may seem harmless, it could end up yielding more costs than benefits. Undigested clinical trial results can be highly misleading in terms of apparent drug benefits as well as drug side-effects. The Drug Watch Web Page initiative therefore merits close scrutiny by anyone interested in drug development, drug therapy and drug safety. It could generate a variety of undesirable effects ranging from unjustified liability attacks and inappropriate switches to older (and less safe) drugs to unfounded promotional activities.

Finally, there is the strong possibility that the FDA is moving toward even greater caution in approving new drugs and in the requirements it imposes on the clinical trials necessary to gain marketing approval. Certainly, this prospect is being widely discussed in the drug development community.

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